IN THE SPECIFICATION:

In the Specification, please amend the following indicated paragraphs as indicated below. Substitute paragraphs are marked up to show changes.

Please amend the paragraph beginning at page 1, line 28 of the as-filed specification as follows:

The direct anti-proliferative effect of GnRH agonists and GnRH antagonists ~~on e.g.~~ on, e.g., prostate carcinomas, mammary carcinomas, and ovarian ~~carcinomas~~ carcinomas, has been confirmed by clinical studies. Some of the GnRH agonists employed in these treatments having a direct anti-proliferative effect are known by the following trademarks of the medicaments approved in Germany: for example ~~Zoladex®, Zoladex 10,8®, Zoladex Gyn®, Profact® Depot, Profact pro injectione/nasal, Synarela®, Enantone Monats Depot®, Uno Enantone®, Enantone Gyn Monats Depot®, Trenantone®, Suprecur®, Carcinil®, or Decapeptyl® 0,5 mg/0,1 mg, Decapeptyl® Depot, Decapeptyl® Gyn as well as Decapeptyl® Diagnostik~~ ZOLADEX®, ZOLADEX 10.8®, ZOLADEX GYN®, PROFACT®-DEPOT, PROFACT® PRO INJECTIONE/NASAL, SYNARELA®, ENANTONE MONATS-DEPOT®, UNO-ENANTONE®, ENANTONE GYN MONATS-DEPOT®, TRENANTONE®, SUPRECUR®, CARCINIL®, or DECAPEPTYL® 0.5 mg/0.1 mg, DECAPEPTYL® DEPOT, DECAPEPTYL® GYN as well as DECAPEPTYL® DIAGNOSTIK. An example for a GnRH antagonist examined in several studies is ~~Cetrorelix®~~ CETRORELIX®, which is not yet approved as a medicament in Germany. Treatment with ~~Cetrorelix®~~CETRORELIX® bears the disadvantage that no depot preparation exists which would be ~~active e.g.~~ active, e.g., for weeks. Other examples of GnRH antagonists used experimentally are ~~Antarelix®~~ANTARELIX® and ~~Antide®~~ANTIDE®, the latter also existing in one embodiment as an oral presentation form. (Russel-Jones et al., 1995, Bioconjugate Chem. 6, 34-42).

Please amend the paragraph beginning at page 4, line 26 of the as-filed specification as follows:

About 30% of patients with recurrent Glioblastoma multiforme showed constant size or shrinking, respectively, of the inoperable residual brain tumor under sustained high-dosage of ~~Tamoxifen®~~ Tamoxifen, an anti-estrogen preparation. This tumor-inhibiting effect in glioblastoma treatment has not been attributed to its anti-estrogenic effect but to its inhibition of protein kinase C (an intracellular signal mediator); cf. Puchner et al., Zentralblatt für Neurochirurgie, Supplement 1996, 47. Jahrestagung Deutsche Gesellschaft für Neurochirurgie, page 44; Pollack et al., 1995, The Efficacy of Tamoxifen as an anti-proliferative Agent in vitro for Benign and Malignant Pediatric Glial Tumors, Pediatr. Neurosurgery 22, 281-288). Moreover, ~~tamoxifen®~~ Tamoxifen is said to increase the sensitivity of tumor cells for platinium-containing therapeutics as well as for radiotherapy.

Please amend the paragraph beginning at page 5, line 6 of the as-filed specification as follows:

For Glioblastoma multiforme (WHO grade IV astrocytoma) and for glioma with a lower grade of malignancy (WHO grade II-IV ~~astrocytoma)~~ astrocytoma), steroid hormone receptors have been observed in a smaller percentage of the cases (cf. Paoletti et al., 1990, J. Neurosurgery, Characteristics and biological role of steroid hormone receptors in neuroepithelial tumors, 73, 736-742). Up to now, an indirect anti-proliferative effect in the case of Glioblastoma multiforme and glioma grade II-IV has been observed in clinical studies in only about 30% of the cases by a response of the tumor to ~~Tamoxifen®~~ Tamoxifen (an anti-estrogen ~~preparation)~~ preparation).

Please amend the paragraph beginning at page 7, line 15 of the as-filed specification as follows:

In a particularly preferred embodiment, fresh human tumor tissue is ~~collected for example~~ collected, for example, during brain tumor surgery (preoperatively) followed by storage in liquid nitrogen. For GnRH receptor determination, the frozen tissue samples are ground and homogenized. In a centrifugation step, the samples are separated from larger tissue debris. The supernatant is again centrifuged. The resulting sediment (pellet) contains the membrane fraction which is again

which is again homogenized to obtain an as homogenous membrane suspension as possible. The membrane suspension is used in the radio receptor assay for determination of GnRH receptors. First, the protein concentration in the membrane fraction prepared is determined photometrically in a conventional and known ~~manner e.g.~~ manner, e.g., using the BioRad protein assay (BioRad, Munich). Determination of the GnRH receptor concentration is performed using a known GnRH agonist, such as ~~Buserelin®~~ Buserelin binding specifically to GnRH receptors in the membrane fraction prepared. Since the GnRH agonist has been radiolabeled, for example by ^{125}I, the concentration of bound radiolabeled GnRH agonist mirrors the concentration of GnRH receptors in the membrane fraction. The concentration of bound radiolabeled GnRH agonist is determined by means of radioactive counts per minute. Both low affinity/high capacity and high affinity/low capacity GnRH receptor binding sites are evaluated (cf. Baumann, K., et al., 1993, Breast Cancer Research Treatment, vol. 25, page 37-46).

Please amend Table I, beginning at page 9, line 1 of the as-filed specification, as follows:

Table I

List of GnRH agonists and GnRH antagonists which may be employed in the treatment of a tumor having GnRH receptors and originating in brain and/or nervous system and/or the meninges and/or of Kaposi sarcoma:

GnRH agonists: ~~Pharmacological substance name~~	GnRH antagonists: ~~Trade mark~~
Leuprorelinacetate, Leuprorelin	~~Cetrorelix®,~~ Cetrorelix, Asta Medica AG, Frankfurt/Main
Triptorelinacetate, Triptorelin	~~Antarelix®,~~ ANTARELIX®, Asta Medica Frankfurt/Main
Buserelinacetate, Buserelin	~~Antide®,~~ ANTIDE®, Ares Sarono Int. SA, Genè Switzerland
Goserelinacetate, Goserelin	~~Ramorelix®,~~ RAMORELIX®, Hoe013HoechstG Frankfurt/Main, Germany

Please amend the paragraph beginning at page 9, line 14 of the as-filed specification as follows:

The minimum treatment dose of the GnRH agonists in the above list correspond to the dosage cited in the ~~Rote Liste®~~ ROTE LISTE® for the respective GnRH agonists for other indications of use for the subcutaneous or the intramuscular administration form, respectively. For intravenous administration of GnRH agonists the minimal daily dose is employed, cf. for ~~example~~ example, Klijn et al., 1982, The Lancet, 1213-1216.

Please amend the paragraph beginning at page 9, line 19 of the as-filed specification as follows:

The minimum treatment dose of the GnRH antagonists ~~Cetrorelix®, Antrarelix®, Antide®, and Ramorelix®~~ Cetrorelix, ANTRARELIX®, Antide, and Ramorelix for subcutaneous and intramuscular administration forms in the above-cited list corresponds to the dosage described in the literature and used with other indications, cf. for ~~example~~ example, for ~~Cetrorelix®:~~ Cetrorelix: Gonzalez-Barcena et al., 1994, The Prostate 24, 84-92.

Please amend the paragraph beginning at page 10, line 3 of the as-filed specification as follows:

The minimum treatment dose of the GnRH agonists ~~Cetrorelix®, Antrarelix®, Antide®, and Ramorelix®~~ Cetrorelix, ANTRARELIX®, Antide, and Ramorelix for the intravenous administration form in the above-cited list corresponds to the dosage which is known for other indications at the proper approval board or described in the Deutsche Pharmazeutische Stoffliste or in the literature and is administered, for ~~example for Antide®:~~ example, for Antide: Fattinger et al., 1996, Am. J. Physiol. 271 (Endocrinol. Metab. 34) E775-E787. The same is true for the GnRH antagonists as described in US patent 5,480,969, UK patent GB 2 246782 B, and US patent 5,198,533.

Please amend the paragraph beginning at page 10, line 10 of the as-filed specification as follows:

According to the invention, GnRH agonists and/or GnRH antagonists may be employed in any suitable form. For tumors within the blood-brain-barrier, direct injection, e.g. into the circulation, intraarterially directly into the nervous system circulation or intravenously, or injection in the liquor ways or local application in the tumor bed following surgery, directly after macroscopic tumor resection, peroperatively or with ~~Ommaya®~~ OMMAYA® reservoir, or another form of subcutaneous ventricular injection in the liquor ways is preferred. It is possible to use both GnRH agonists and GnRH antagonists because both bind as ligands to the GnRH receptor. Further, ligands which are specifically directed to the GnRH receptor may be ~~used e.g.~~ used, e.g., preferably human or humanized antibodies. In most cases it is preferable to ensure that the targeting agent primarily reaches tumor cells. Therefore imaging methods using the ligand with tracers are a further aspect of the invention. If the ligand is localized mainly in the tumor, the ligand may be coupled to a cytotoxic agent, such as a radioisotope or another toxic substance such as ricin A or the like. Preferred GnRH agonists are cited in the ~~Rote Liste~~ ROTE LISTE®, which is explicitly incorporated herein by reference (Rote Liste, 1997, paragraph 50, part 3, pituitary hormones, 50038 to 50056, editor ROTE LISTE® Service GmbH, Frankfurt/Main). Preferred GnRH antagonists ~~which~~ that already have been clinically used in patients for other treatments are ~~Cetrorelix® and Antarelix®~~ Cetrorelix and ANTRARELIX® from Asta Medica AG, Frankfurt/Main, Germany, and ~~Antide®~~ Antide from Ares-Sarono Int. AG, Lausanne, Switzerland.

Please amend the paragraph beginning at page 11, line 5 of the as-filed specification as follows:

In a particular embodiment, the GnRH agonists or GnRH antagonists are conjugated with a gonadotropin or LH inhibitor, respectively, such as ~~Gossypol®~~ GOSSYPOL® (cf. Flack et al., 1993, J. Endocrinol. Metab., Oral Gossypol in the Treatment of Metastatic Adrenal Cancer 76, 1019-1024; Poso, H., et al., The Lancet, 1980, 885) or with melatonin or a melatonin analogue (an agonist or antagonist)

(an agonist or antagonist) (cf. Lissoni et al., 1996, Increased Survival Time in Brain Glioblastomas by a Radioneuroendocrine Strategy with Radiotherapy plus Melatonin Compared to Radiotherapy Alone, Oncology 53, 43-46).

Please amend the paragraph beginning at page 11, line 13 of the as-filed specification as follows:

For the first time, the GnRH receptor concentration in cell membranes of human brain or nervous system tumor cells, ~~i.e.~~ i.e., the GnRH receptors on the membrane which are effective in vitro have been determined using a radio receptor assay. With the method according to the invention, the biological activity or specifically the active GnRH receptors, respectively, are determined. For this purpose, radiolabeled ~~BUSERELIN,~~ Buserelin, a GnRH agonist, is used as a marker binding specifically to GnRH receptors. Based on radioactive counts of bound ~~BUSERELIN~~ Buserelin, the GnRH receptor concentration may be determined. This detection has already been used for other tumors such as mammary carcinoma and the like. The method used according to the present invention measures the GnRH receptor concentration on cell membrane extracts of fresh human tumor tissue.

Please amend the paragraph beginning at page 15, line 23 of the as-filed specification as follows:

According to the invention, the GnRH agonists or GnRH ~~antagonists~~ antagonists, as well as the conjugated GnRH agonists or GnRH antagonists are used to treat tumors originating in brain and/or nervous system and/or the meninges, for ~~example~~ example, Glioblastoma multiforme. The medicaments according to the present invention may be prepared in any manner known to the skilled artisan, in ~~particular~~ particular, for subcutaneous, intramuscular, intravenous, intraspinal or subdural, respectively, or intranasal application or in the form of a sustained release implantation. The medicaments according to the present invention may also be administered via a subcutaneous ventricular cytostatic reservoir being connected to the ventricle wherein the reservoir may be replenished by injections through the skin. The GnRH agonists may be administered in the same dosage as those ~~which are for example~~ that are, for example, used in the treatment of prostate, ~~mamma~~ mammary carcinoma or endometriosis; cf. e.g. Rote Liste, 1997, paragraph 50, part 3, hypothalamic hormones, 50038 to

Liste, 1997, paragraph 50, part 3, hypothalamic hormones, 50038 to 50056, Editor ROTE LISTE® Service GmbH, Frankfurt/Main, which is included herein explicitly by reference; cf. Annex A. The minimal dose corresponds to the dose cited in the Rote Liste for the respective GnRH agonists. For example, in the case of intraspinal or subcutaneous ventricular administration via a cytostatic ~~reservoir~~ reservoir, the minimal dosage may be lower than that cited in the Rote Liste for the respective GnRH agonists. The maximal dose corresponds to the LD_{50} value for the respective GnRH agonists. The dosage may be optionally increased or decreased following a finding of the GnRH receptor concentration obtained in a neurological manner. The frequency of application or daily dose, respectively, may also be found in the Rote Liste. Preferably, the medicaments are administered until complete remission (regression) of the tumor which may be evaluated neuroradiologically and clinically.

Please amend the paragraph beginning at page 16, line 15 of the as-filed specification as follows:

For subcutaneous administration, ~~e.g. Carcinil®, Decapeptyl® 0,5 mg/0,1 mg~~ e.g., CARCINIL®, DECAPEPTYL® 0.5 mg/0.1 mg or Uno-Enantone may be employed. As sustained release ~~implantations for example Profact® Depot, Zoladex®, or Enantone Monatsdepot~~ implantations, for example, PROFACT®-DEPOT, ZOLADEX®, or ENANTONE MONATS-DEPOT® may be administered. For intramuscular administration, ~~e.g. Decapeptyl® Depot, Decapeptyl® Gyn,~~ e.g., DECAPEPTYL®-DEPOT, DECAPEPTYL®-GYN, or Enantone-Gyn may be employed. For intranasal ~~administration e.g. Profact® Nasal, Suprecur® Nasal, or Synarela® Nasal~~ administration, e.g., PROFACT®-NASAL, SUPRECUR®-NASAL, OR SYNARELA®-NASAL may be used. For intravenous administration or intranasal administration, respectively, for ~~example Profact~~ example, PROFACT® pro injectione/-nasal may be administered in the dosage given by Klijn, J.G., and De Jong, F.H. in Klijn, J.G., and De Jong, F.H., 1982, The Lancet, 1213-1216. The GnRH antagonists may be administered in a dosage which has ~~been~~ been, for ~~example~~ example, given for ~~Cetrorelix®~~ Cetrorelix in Gonzalez-Barcena et al., 1994, The Prostate 24, 84-92, or may be administered at minimum in the dosage as ~~given for example for Antide®~~ given, for example, for Antide in Fattinger et al., 1996, Am. J. Physiol. 271 (Endocrinol. Metab. 34: E775-E787).

Please amend the paragraph beginning at page 17, line 2 of the as-filed specification as follows:

As an example for the determination of the concentration of GnRH receptors on cell membrane extracts of cell lines and/or cell cultures, the ~~Decapeptyl®~~ DECAPEPTYL® radio receptor assay is used with membranes (as described by Emons, G., et al., 1993, Cancer Research 53, 5439-5446). According to this protocol, the GnRH receptors are determined on a human cell line such as the human glioblastoma cell line U-87 MG or U-373MG (Pinski et al., 1994, Cancer Research 54, 5895-5901). In this test, the low affinity/high capacity as well as the high affinity/low capacity GnRH receptor binding sites are evaluated. Similar results as those described in Emons, G., et al., supra, for the cell lines EFO-21 and EFO-27 are obtained.

Please amend the paragraph beginning at page 18, line 9 of the as-filed specification as follows:

A human cell line such as the ~~well-known~~ well-known human glioblastoma cell lines U-87MG or U-373MG (Pinski et al., supra) or a human cell line such as the ~~well-known~~ well-known Kaposi sarcoma cell lines KSY-1 or KS-SLK (Parkash et al., 1996, New England Journal of Medicine, 335, 17, ~~1261-1269)~~ 1261-1269), or a human cell line such as the ~~well-known~~ well-known human malignant melanoma cell line MV3 or BLM (Goldbrunner, R.H., et al., 1996, Anticancer Research 16 (6B), 3679-87) or a human medulloblastoma cell line such as the ~~well-known~~ well-known cell line Daoy or D283 MED (Stockhammer et al., 1995, J. Neurosurgery, 83, 672-681) or human meningeoma cell cultures (Boyle-Wash, E., et al., 1995, Journal of Endocrinology, 145, ~~155-161)~~ 155-161), are cultured as described by the above-mentioned authors for the above-mentioned cell lines and then treated as described by Emons, G., et al., 1993, supra, and Irmer, G., 1995, supra, with a concentration of the GnRH agonist Triptorelin, GnHR antagonist SB-75 ~~(Cetrorelix®)~~ (Cetrorelix) or GnRH antagonist ~~Ramorelix®~~ Ramorelix as described therein. Similar results to those described by Emons et al., Cancer Research, 53, 1993, 539-544, and Irmer, G., et al., supra, were obtained.

Please amend the paragraph beginning at page 18, line 23 of the as-filed specification as follows:

Separately, the above-mentioned cell lines were also treated with ~~an~~ a GnRH agonist, either with Goserelin ~~(Zoladex®,~~ (ZOLADEX®, Buserelin or Leuprorelin) or with a GnRH antagonist such as ~~Antide® or Antarelix®.~~ Antide or ANTRARELIX®. Similar anti-proliferative effects as those described by Pinski et al. or Irmer et al., supra, were observed.

Please amend the paragraph beginning at page 18, line 27 of the as-filed specification as follows:

Also separately, such cell lines were additionally ~~treated~~ treated, each with one of the GnRH antagonists ~~Cetrorelix®, Antarelix®, Antide®, and Ramorelix®~~ Cetrorelix, ANTRARELIX®, Antide, and Ramorelix, or with one of the GnRH antagonists as described in US patent 5,480,969, US patent 5,198,533, or UK patent GB 2 246782 ~~B~~ B, wherein this treatment was performed similar to that reported in Emons et al., supra, for SB 75 (Cetrorelix®). A similar anti-proliferative effect occurs.

Please amend the paragraph beginning at page 19, line 11 of the as-filed specification as follows:

An effect of the treatment of tumor-implanted nude mice (Pinski et al., ~~supra)~~ supra), each with one of the GnRH agonists Buserelin, Triprorelin, Goserelin, and Leuprorelin and each with one of the GnRH antagonists ~~Cetrorelix®~~ Cetrorelix (SB-75), ~~Antarelix®, Antide®, and Ramorelix®~~ ANTRARELIX®, Antide, and Ramorelix on the growth of malignant gliomas U-87 MG and U-373MG was proven by us using daily doses and controls in nude mice as have been described for the determination of the efficacy of similar peptides in Pinski et al., supra. Similar growth-inhibiting effects could be observed in the above tumors by treatment with the GnRH agonists and GnRH antagonists mentioned by us.

Please amend the paragraph beginning at page 20, line 5 of the as-filed specification as follows:

~~2~~ Two Patients with inoperable, stereotactically confirmed Glioblastoma multiforme after conventional radiotherapy were treated under permanent medication with ~~Zoladex®~~ ZOLADEX® in the dosage and administration form as cited for metastasizing ~~mamma~~ mammary carcinoma in the Rote Liste. MRT controls reveal a significant reduction in tumor volume.

Please amend the paragraph beginning at page 20, line 11 of the as-filed specification as follows:

Patients with histologically confirmed Glioblastoma multiforme after a first operation were treated (randomized controlled) with ~~Zoladex®~~ ZOLADEX® as described by Jonat et al., 1995, European J. Cancer, 137-142. Following radiotherapy, they are assigned to two groups. One group is treated with ~~Zoladex®~~ ZOLADEX® and one group without ~~Zoladex®~~ ZOLADEX® (or with ~~Cetrorelix®~~ Cetrorelix and without ~~Cetrorelix®,~~ Cetrorelix, or with ~~Antide®~~ Antide and without ~~Antide®,~~ Antide, or with ~~Decapeptyl®~~ DECAPEPTYL® or without ~~Decapeptyl®~~ DECAPEPTYL®, etc.). The effects are similar to the metastasized perimenopausal ~~mamma~~ mammary carcinoma. The percentage showing an actual significant ~~therapy~~ therapeutic effect is evaluated according to the criteria of tumor volume, recidivation-free survival, overall survival following initial application and Karnofsky and Spitzer indices in a clinical neurological examination and under consideration of the other examination criteria (Sposto, R., et al., 1989, J. Neurooncology, 7, 165-177, and Kirby, S., et al., 1995, J. Natl. Cancer Institute, 87, 1884-1888, 1995). In MRT and/or CAT scan, a significantly higher reduction in tumor volume or significantly longer recidivation-free survival and significantly longer overall survival following initial application, respectively, than in the control group not treated with ~~Zoladex®~~ ZOLADEX® have been observed.

Please amend the paragraph beginning at page 25, line 21 of the as-filed specification as follows:

Referring to Fig. 1: For Antide (GnRH antagonist) a clear inhibition of proliferation is seen in the high concentrations of 10^{-4} M and 10^{-5} M of 15% and 35%, respectively, (similar ~~as~~ to that described by Emons et al., 1993, supra, but with later onset as compared to the ovarian carcinoma cell lines used therein in which an anti-proliferative effect of the antagonists in one of the two cell lines occurred from day 1 on). At a concentration of ~~10^{-6} M~~ 10^{-6} M, no inhibition of the proliferation was observed but a stimulation of the growth of 40%. This paradox in vitro effect of GnRH antagonists is similar to that described in Limonta et al., 1993, J. Clin. Endocrinol. Metab., 76, 839-845, for prostate carcinomas with GnRH receptors. A similar in vitro effect for relatively low concentrations is also known for tamoxifen in the MCF-7 ~~mamma~~ mammary carcinoma cell line (Zänker, K., et al., 1995).